Antiepileptic drugs

Assistant prof./ Heba Ahmed Hassan
Clinical Pharmacology Department Mutah University
Faculty of Medicine

Epilepsy

Def: A chronic disorder characterized by recurrent spontaneous seizures due to abnormal discharge of cerebral neurons.
Consists of 3 phases: 1- Aura—early part of a seizure, may include odd smells or tastes. 2- Ictal—time from first symptom to end of seizure activity. 3- Postictal—period of gradual recovery back to pre-seizure baseline level of function/awareness.

Types:

ILAE 2017 CLASSIFICATION OF SEIZURE TYPES BASIC VERSION

FOCAL ONSET

AWARE | IMPAIRED AWARENESS

MOTOR ONSET
NONMOTOR ONSET

FOCAL TO BILATERAL TONIC-CLONIC

GENERALIZED ONSET

MOTOR

TONIC-CLONIC | OTHER MOTOR

NONMOTOR (ABSENCE)

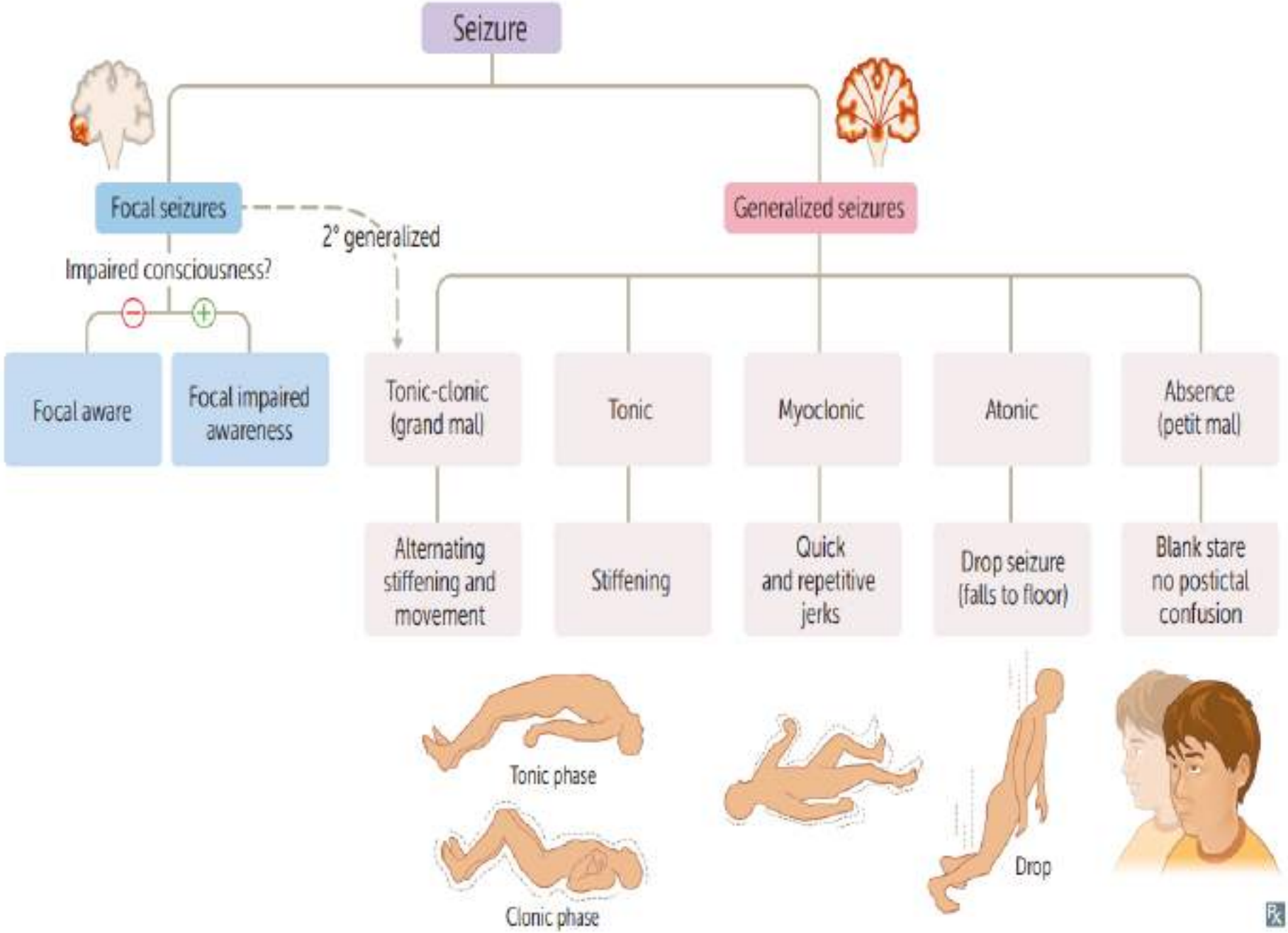
UKNOWN ONSET

MOTOR

TONIC-CLONIC | OTHER MOTOR

NONMOTOR

UNCLASSIFIED


Seizure
Focal seizures
2° generalized
Impaired consciousness?
Focal aware
Focal impaired awareness
Generalized seizures
Tonic-clonic (grand mal)
Tonic
Myoclonic
Atonic
Absence (petit mal)
Alternating stiffening and movement
Stiffening
Quick and repetitive jerks
Drop seizure (falls to floor)
Blank stare no postictal confusion
Tonic phase
Clonic phase
Drop

Cellular Mechanisms of Seizure Generation

- **Excitation (too much)**
  - Ionic-inward Na^{+}, Ca^{++} currents
  - Neurotransmitter: glutamate, aspartate

- **Inhibition (too little)**
  - Ionic-inward Cl; outward K^{+} currents
  - Neurotransmitter: GABA

Mechanism of action of antiepileptic drugs

1. Reduction of cell membrane permeability to Na

e.g., phenytoin, carbamazepine, valproate & lamotrigine.

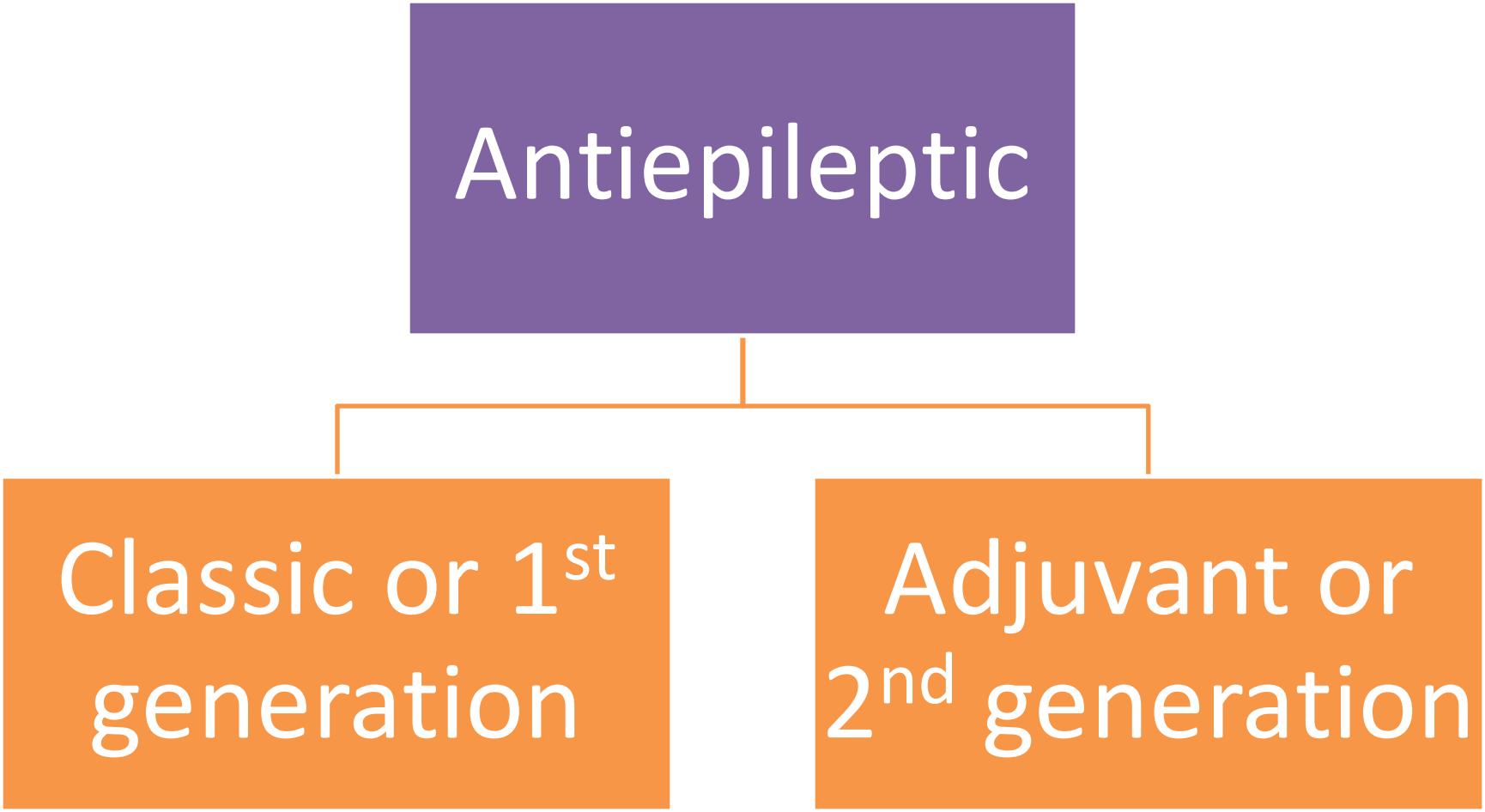
2. Block of voltage-dependent T-Calcium channels

e.g., ethosuximide, valproate.

3. Modifying neurotransmitters:

A. Enhancement of GABA-mediated synaptic inhibition *e.g. barbiturates, benzodiazepines, vigabatrin & valproate*.

B. Decreased excitatory amino acid function *e.g. felbamate and toprimate*



Due to high toxicities of most antiepileptic drugs, monotherapy is preferred and only used Only add on therapy in unresponsive cases or refractory epilepsy

I- Phenytoin and Fosphenytoin

Pharmacokinetics:

A: Oral absorption is **complete**.

D: pass blood brain barrier and placenta

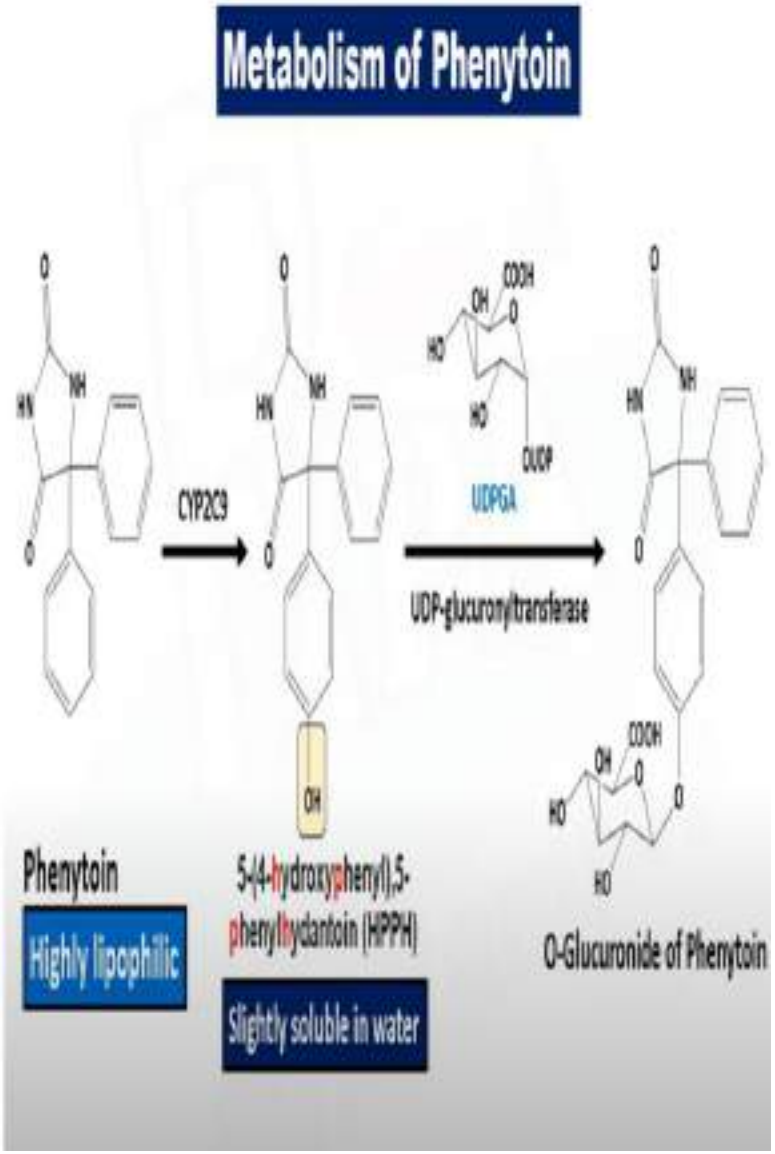
About 90% bound to **plasma protein.**

- T1/2 = 12-36 hours.

M: It is **hydroxylated** in the liver and this needs **folic acid** as cofactor THEN glucuronation to final metabolites

E: Elimination follows **saturable** kinetics.

NOTE: Fosphenytoin: **prodrug (water soluble)** of phenytoin, available for **parentral** use in **status epilepticus (i.v or i.m).**

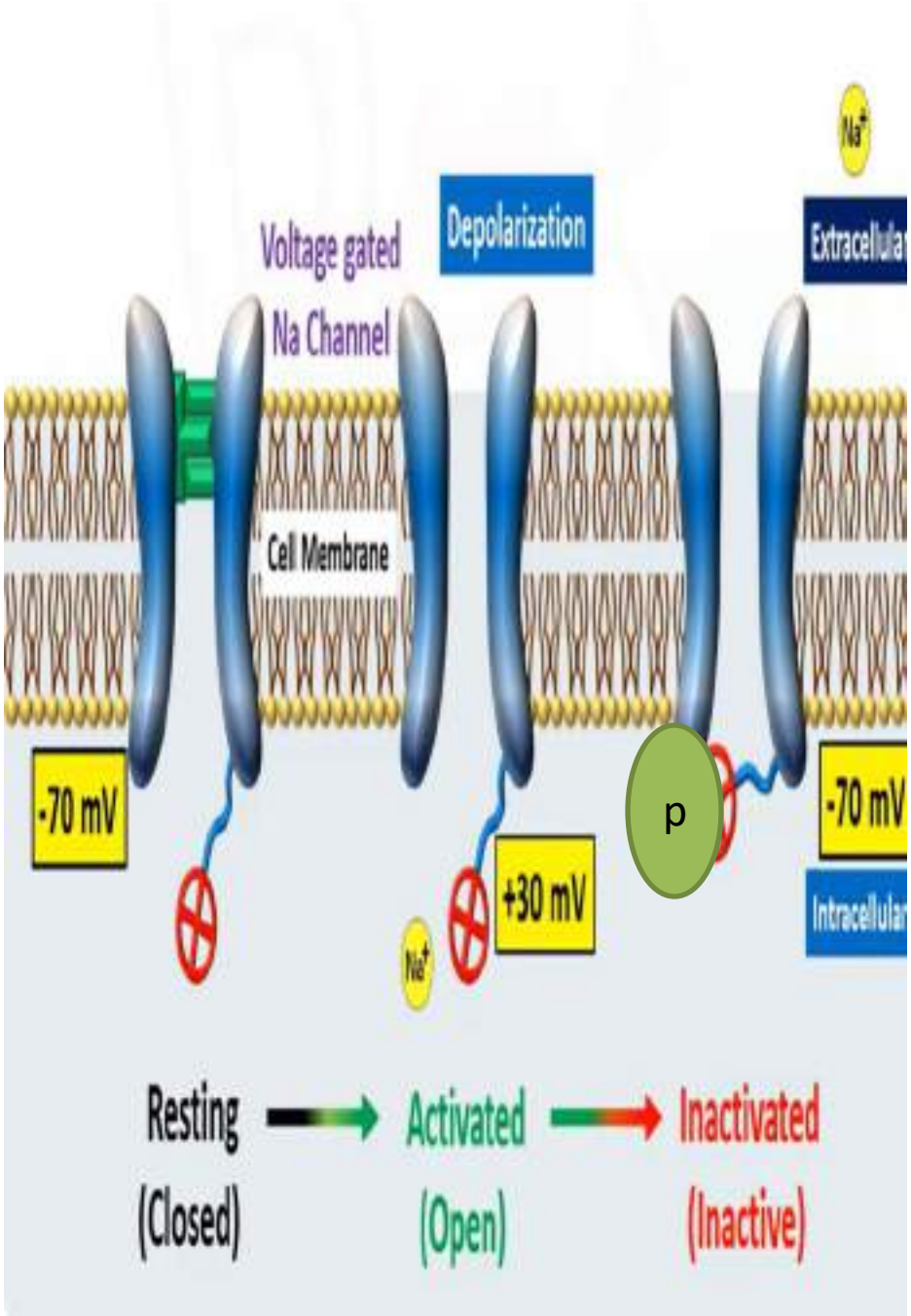


- **Mechanism of action**

➢ It blocks voltage-gated **Na+ channels**.

➢ At higher concentrations. It can block voltage-dependent **Ca++ channels**

➢ interferes with the **release of neurotransmitters**.



Pharmacological actions:

1. Antiepileptic: It has a selective antiepileptic action without causing CNS depression.

2-Antiarrhythmic: (Class IB antiarrhythmic)

It depresses automaticity, excitability & increased conduction velocity, so abolish reentry arrhythmias.

Therapeutic uses:

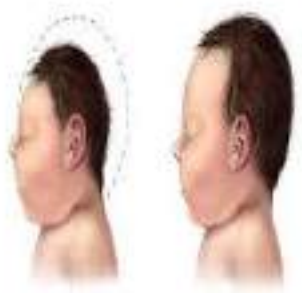
1. Antiepileptic:

A. focal seizures

B. Status epilepticus (Fosphenytoin).

2. Ventricular arrhythmia.

Side effects



1. C.N.S: Nystagmus, diplopia, ataxia & vertigo.
2. Liver: enzyme **inducer**
3. Blood: Megaloblastic anemia

it interferes with folate absorption and/or metabolism.

4- **Teratogenicity:**

- If taken in the first trimester, cleft palate and hare lip (fetal hydantoin syndrome).
- Cardiac septal defect
- Hypoprothrombinemia of the baby, if taken before labor.
- Neural tube defect (spina bifida)

5. **Gingival hyperplasia.**

6. **Hypersensitivity reactions** **such** as rash, fever, and **lymphadenopathy**.

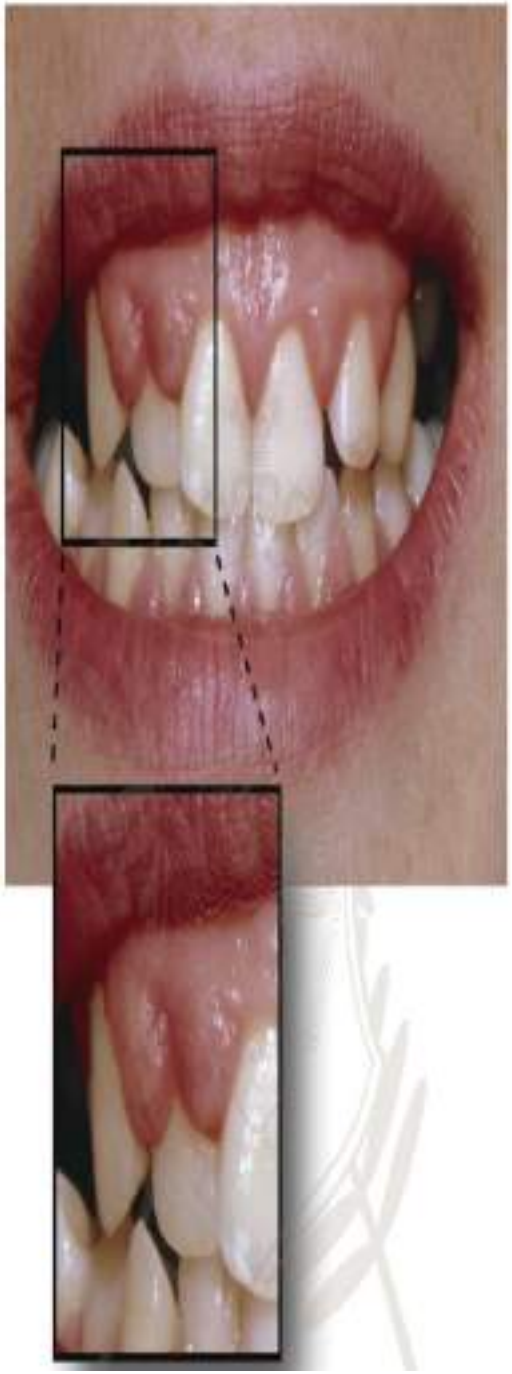
7. **Hirsutism and acne** due to increased androgen secretion

8. **Osteomalacia with hypocalcemia**

- occurs with chronic use (it interferes with vitamin D hydroxylation and reduces G.I. absorption of calcium).

9. **Inhibit insulin release** (hyperglycemia)

10. Neuropathies due to folate deficiency



HOW TO REMEMBER *SIDE EFFECTS OF PHENYTOIN*

IN 2 MINS

H	HIRSUTISM
O	OSTEOMALACIA
T	TERATOGENICITY
M	MEGALOBLASTIC ANEMIA
A	ARRHYTHMIA (at toxic doses)
I	INHIBITS INSULIN RELEASE
L	LYMPHADENOPATHY
G	GUM HYPERTROPHY
A	ATAXIA (at toxic doses)
N	NYSTAGMUS (at toxic doses)
D	DIPLOPIA (at toxic doses)
K	VITAMIN K DEFICIENCY

FETAL HYDANTOIN SYNDROME

- Cleft Lip
- Cleft Palate
- Microcephaly
- Hypoplastic phalanges

Drug interactions of phenytoin:

1. Displacement of phenytoin from plasma proteins: phenylbutazone, oral anticoagulants & sulfonamides.

2. Inhibition of phenytoin metabolism by chloramphenicol & valproic acid.

3. Phenytoin metabolism is enhanced by enzyme inducers: carbamazepine and phenobarbitone.

4. Phenytoin (enzyme inducer) can increase the metabolism of ***warfarin*** and ***steroids.***

Precautions:

1. **Serum level** monitoring is essential.
2. **Oral hygiene** (frequent brushing, gum massage).
3. **Vit D and folate** supplements should be given when necessary.

II- Carbamazepine and oxcarbamazepine (TCA-related)

- **Pharmacokinetic:**

A: Following oral absorption

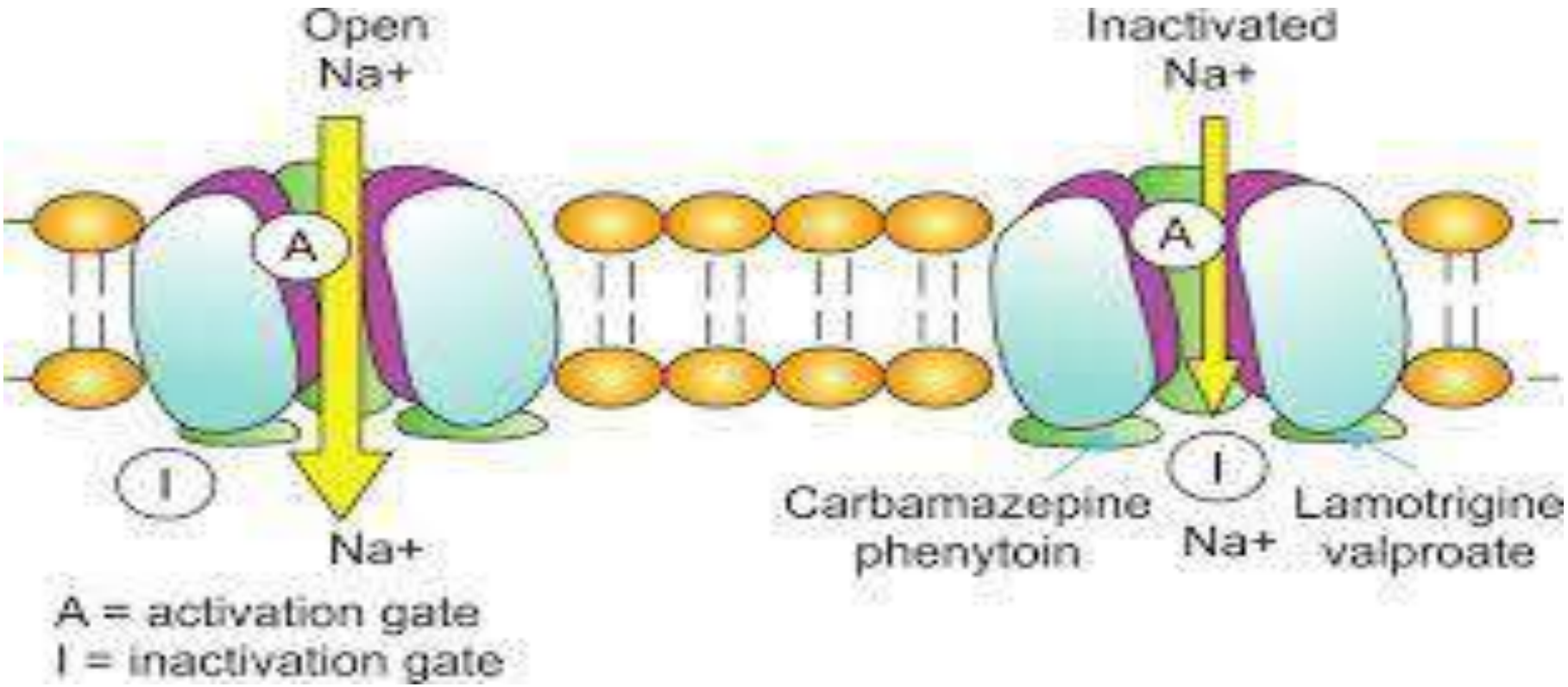
D: it enters the brain rapidly, cross placenta, bound to plasma protein

M: It **induces** hepatic microsomal enzymes.

Its half life decreases with chronic administration due to auto- induction

- The enhanced activity of liver microsomal enzymes also increases metabolism of many other drugs including anti-epileptics

- **Mechanism of action**
- It **blocks the Na+ channel, thereby reducing** the propagation of abnormal impulses in the brain.



• Therapeutic uses:

1. Focal seizures.
2. Trigeminal neuralgia.
3. Cerebral or nephrogenic diabetes insipidus

• Side effects:

1- C.N.S: Nustagmus, Diplopia, Ataxia & **drowsiness**.

2 . Liver dysfunction

3. Blood: Aplastic anemia, agranulocytosis (causes bone marrow depression).

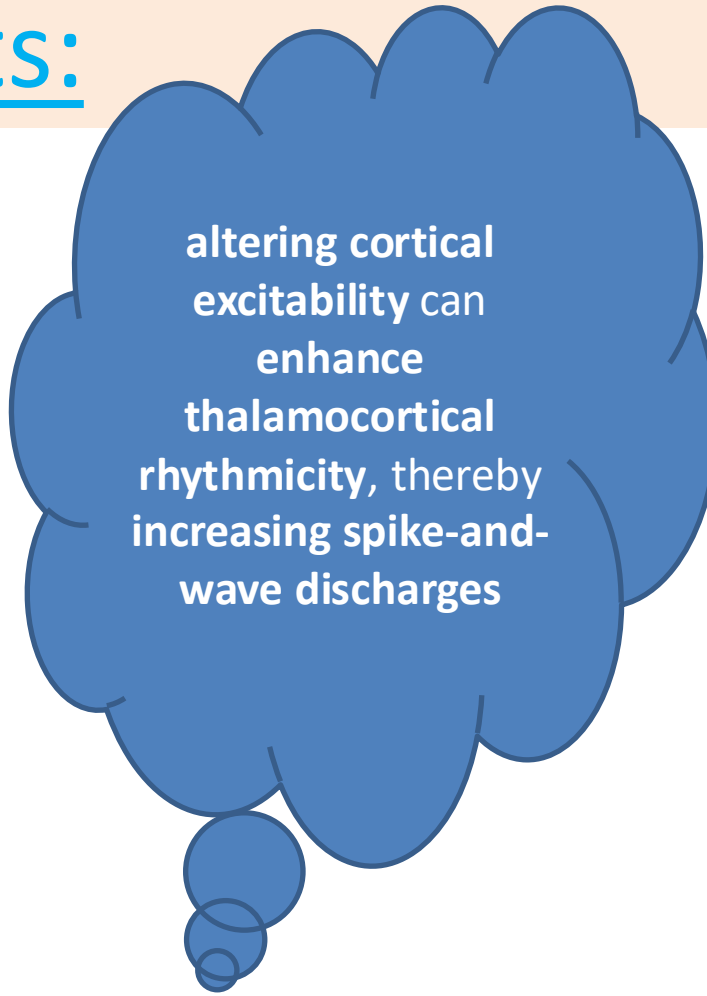
Teratogenicity: craniofacial anomalies and spina bifida

2. G.I.T: nausea & vomiting.

3. Allergy: rash & photosensitivity.

4. Hyponatremia, water toxicity due to ↑ ADH effects.

5. Not used in the treatment of absence seizures



- **Oxcarbazepine:**

- **It is A prodrug that converts to an active metabolite,** MHD (10-monohydroxy derivative).
- It is an anticonvulsant.
- C.N.S. toxicities are similar to those of carbamazepine, but lesser.
- Lesser hepatic enzyme inducer with no autoinduction.
- There are no reports of hepatic failure or bone marrow abnormality.
- More pronounced hyponatremia.

III- Valproic acid, valproate, divalproex

- **Pharmacokinetics:**
  - Well absorbed orally.
  - 90% bound to plasma proteins.
  - Metabolized in the liver to toxic metabolites.
- **Mechanism of action:**
- It acts by increasing GABA concentrations in synaptic regions through:

-Inhibition of ***GABA transaminase*** (enzyme that breaks GABA) or

-Inhibition of ***GABA reuptake*** by nerve endings.

- It blocks Na+ channels & T-Ca+ channels.

Therapeutic uses:

1. **Broad** spectrum antiepileptic:

effective in generalized epilepsy & focal seizures but it is not the drug of choice (**sedation** & **hepatotoxicity**).

2. focal seizures **divalproex**
3. Absence epilepsy. **divalproex**
4. Febrile convulsion.
5. Myoclonus and tonic -clonic **divalproex**
6. Prophylaxis of migraine

Side effects:

1. CNS: N,A,D
2. liver: Hepatotoxicity.
3. Teratogenic: more increased incidence of spina bifida of any antiepileptic. Decrease I.Q for child.

4- G.I.T: anorexia, nausea & vomiting.

5- Hair loss (alopecia)

Drug interactions:

- Valproic acid inhibits the metabolism of phenobarbitone, phenytoin and carbamazepine.
- It displaces phenytoin from plasma protein binding sites.

V- Barbiturates (Bb) and benzodiazepine Bz)

- **Phenobarbitone**: it has selective anticonvulsant activity & it may act through **potentiating the inhibitory pathway (GABA).**

.**Diazepam, Clonazepam & Lorazepam** : drug of choice for treatment of status epilepticus (rapid onset).

IV- Ethosuximide (LEAST TOXIC ANTIEPILEPTIC)

- **Pharmacokinetics**:
  - Well absorbed orally.
  - Not bound to plasma protein.
  - 75% are metabolized.
  - 25% are excreted unchanged.
- **Mechanism of action:**

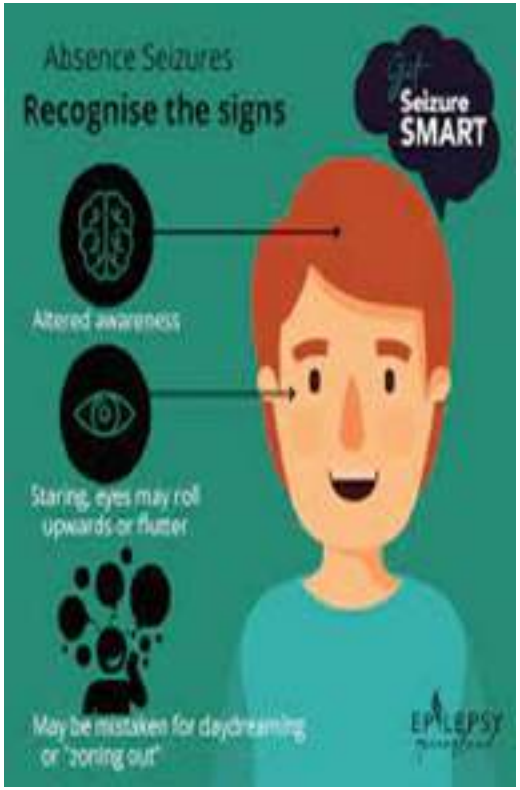
  It blocks voltage-gated **T-Ca++ channels.**
- **Therapeutic uses:**

  It is the drug of first choice in **absence** seizures

- **Side effects:**

1.G.I.T: nausea, vomiting & diarrhea

2.Allergy: skin rash & urticaria.



Absence Seizure

involves sudden lapse in consciousness and staring blankly into space, the episodes last less than 15 seconds

- Newer antiepileptic drugs (2ND generation)

- All are used as add-on therapy in **refractory** epilepsy.
- Some of them have proven efficacy as **monotherapy.**

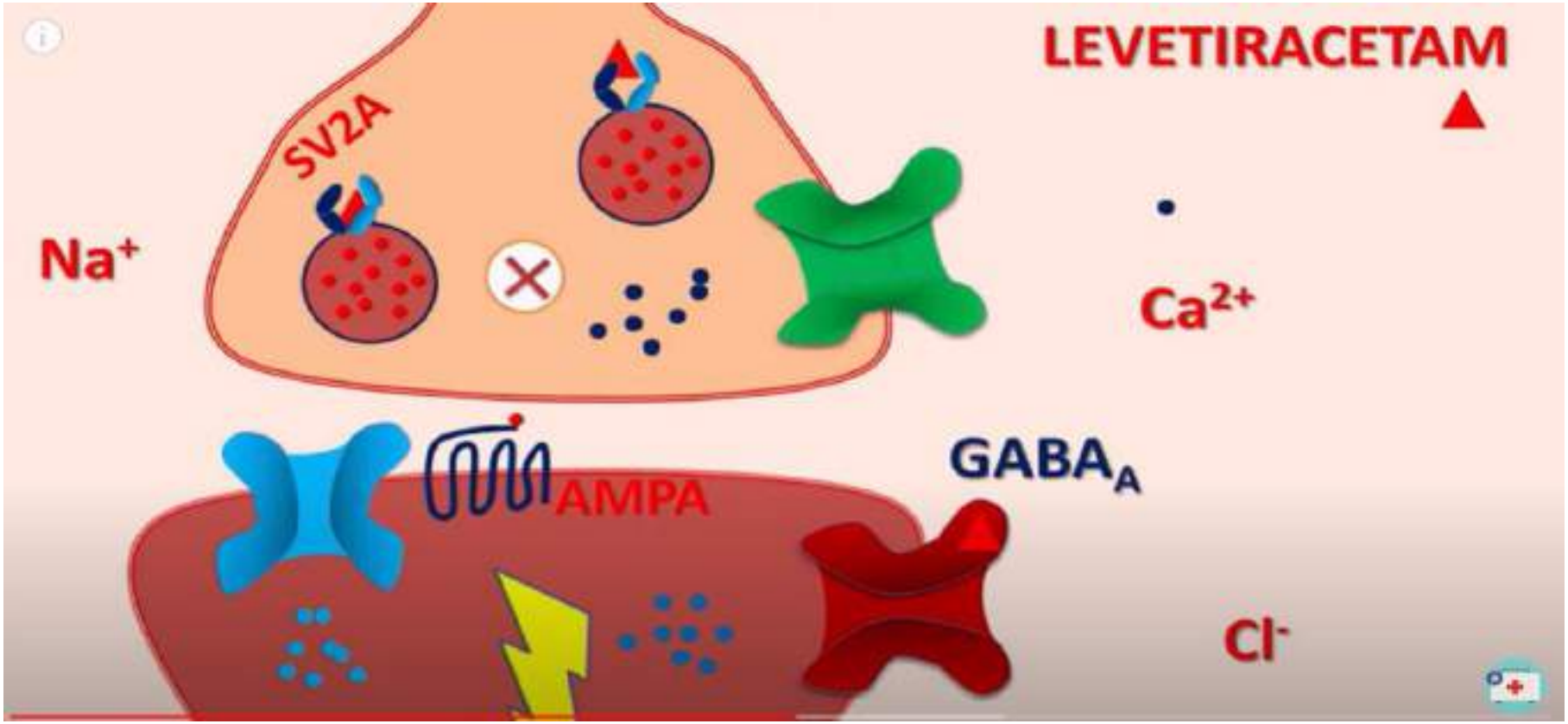
Feature	Old AEDs	New AEDs
Seizure coverage	Narrow to broad	Mostly broad
Side effects	More severe, frequent	Less severe, better tolerated
Drug interactions	Many	Few
Monitoring	Often required	Usually not required
Cost	Low	High

Lamotrigine	Topiramate	Zonisamide (Sulfa)
MOA: blocks Na & Ca++ channels. **used in** all types of epilepsy except status epileptics **Side effects** dizziness, headache & ataxia, Stevens Johnson syndrome	**MOA:** blocks Na & Ca++ channels. Bind glutamate receptor **Used in:** focal, generalized epilepsy and absence seizures **Side effects:** impaired concentration, diplopia, weight loss & kidney stones	**MOA:** Blocks Na+ & Ca++ channels. **Used in:** focal, generalized epilepsy and absence seizures **Side effect:** kidney stones and oligohidrosis.

Gabapentin	Pregabalin	Vigabatrine	Tiagabine
MOA: Enhance release of GABA. They interfere with voltage-dependent Ca++ channels **Uses:** Migraine and **neuropathic pain (post-herpetic neuralgia and diabetic neuropathy)**. Approved as adjunct therapy for focal convulsions **Side effects:** dizziness, headache & ataxia	**MOA:** They interfere with voltage-dependent Ca++ channels inhibit excitatory transmitter release **Used in:** focal seizures **Side effects:** dizziness, headache & ataxia.	**MOA:** It is an irreversible inhibitor of GABA transaminase, increasing the concentration of GABA. **Used in** grand mal and focal seizures(refractory) **Side effects:** sedation, dizziness & behavioral changes, **irreversible vision affection**	**MOA:** It blocks GABA uptake (Transporter) into presynaptic neurons. **Used in:** focal seizures **Side effect:** dizziness & GI upset.

Levetiracetam and brivaracetam

- **MOA:** Modifies the release of glutamate and GABA by binding to the synaptic vesicle protein(SV2A)
- **Used in:** broad spectrum antiepileptic used in all types of epilepsy except stsatus
- **Side effects:** dizziness & sleep disturbances, behavioral changes.



Felbamate

- **MOA:**

It blocks Na+ & Ca++ channels & competes with glycine cofactor at NMDA receptors.

- **Side effects:**

liver and bone marrow toxicities, so it is reserved for use in refractory epilepsy.

AED	Pregnancy Safety	Main Risk
Valproic acid	✗ Avoid	Neural tube defects, cognitive impairment
Carbamazepine	⚠ Moderate	NTDs
Phenytoin	⚠ Moderate	Fetal hydantoin syndrome
Phenobarbital	⚠ Moderate	Vitamin K deficiency bleeding
Lamotrigine	✓ Safe	Low risk cleft palate
Levetiracetam	✓ Very safe	Minimal

Status epilepticus

Def: A medical emergency consisting of prolonged (> 10-minute) or repetitive seizures that occur without a return to baseline consciousness.

Common causes

Include anticonvulsant withdrawal/noncompliance, anoxic brain injury, sedative withdrawal or other drug intoxication, metabolic disturbances (eg, hyponatremia), head trauma, and infection.

Treatment:

Maintain ABCs; consider rapid intubation for airway protection.

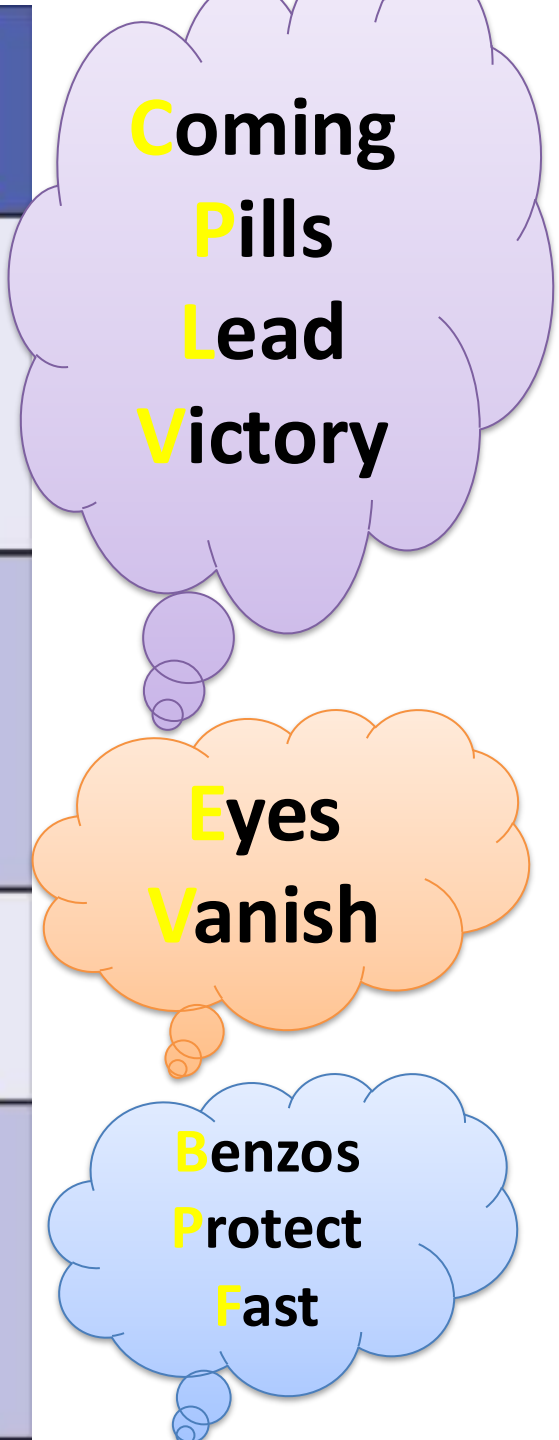
Administer thiamine, followed by glucose and naloxone to presumptively treat potential etiologies.

Give an IV benzodiazepine (lorazepam or diazepam) plus a loading dose of fosphenytoin.

If seizures continue, intubate and load with phenobarbital. .

Initiate a meticulous search for the underlying cause

Seizure Type	Effective Drugs
Partial–simple or complex	Valproic acid, phenytoin, carbamazepine, lamotrigine
General–tonic-clonic	Valproic acid, phenytoin, carbamazepine, lamotrigine
General–absence	Ethosuximide, valproic acid
Status epilepticus	Lorazepam, diazepam, phenytoin, or fosphenytoin*




Thank You